ALZHEIMER'S DISEASE

Dr. Neil Buckholtz

DR. BUCKHOLTZ: I'm going to talk about Alzheimer's disease in terms of the clinical aspects and in terms of the changes in the brain that are going on in Alzheimer's disease. In the last part I would like to talk about what I think are very optimistic directions for the treatment of Alzheimer's disease, both in terms of the memory problems and also in terms of the behavioral problems.

And so what I would like to do to start is just give you an idea of …

(Break in tape.)

DR. BUCKHOLTZ: So, first of all, normal forgetting. As we grow older some of us start to forget things, but this is normal forgetfulness. We all start maybe forgetting a little bit about people's names, some appointments, and most of us deal with this very well in terms of making lists and notes. There are things that produce normal forgetfulness: stress, various distractions that we have, obviously grief, fatigue, poor vision or hearing, use of alcohol, trying to remember too many things at once. So there is normal aging.

Interestingly, when I was listening to some of the conversations before, one person was saying, "Well, you know, as we get older, we all lose brain cells." Well, in fact, that does not seem to be the case. Under normal circumstances, as we get older, we do not lose nerve cells in most parts of the brain. This is something that has come up actually within the past three to five years. It is only under certain circumstances such as the neurodegenerative diseases, where brain cells actually die, and I will be talking to you more about that as we go on.

Dementia is separate from normal aging. In dementia there is decreased recent and long-term memory. This is really the hallmark of all kinds of dementia: reduced ability to think and reason, impairments of judgment, and some changes in personality. There are some treatable causes of dementia, although frankly most of them are not treatable, but it is important to make sure in terms of the diagnosis that we get a good diagnosis because there are some treatable causes.

Depression produces many of the signs that you see in dementia but in fact, depression is treatable in a lot of cases. As you know, as people get older, they start taking a lot of medications and many of these interact with other ones. Many of these produce changes in the brain that are detrimental to learning and memory, so these have to be assessed. There are some nutritional and metabolic disorders, stroke and

hydrocephalus. All of these things need to be determined before a diagnosis of dementia is actually made.

But, unfortunately, there are a number of irreversible dementias. The one that we are going to focus on this morning and the one that is most prevalent is Alzheimer's disease. There are some other ones. Multi-infarct dementia from stroke. Some people with Parkinson's disease get dementia, but not all. And AIDS dementia. Overall, about two-thirds of all dementia in older people results from Alzheimer's disease.

There are a number of early symptoms of Alzheimer's disease. Again, confusion and memory loss is generally considered to be the hallmark, the thing that people pick up on most. There are other aspects: difficulty finding words, getting lost, problems with routine tasks, changes in personality.

I am going to give you at the end a number of Web sites that you can check. The Alzheimer's Association is a very good source of information; they have ten warning signs of Alzheimer's disease, and I will just mention these now. You can go back and look on their Web site later.

1. Memory loss that affects job skills.

2. Difficulty performing familiar tasks.

3. Problems with language.

4. Disorientation to time and place.

5. Poor or decreased judgment.

6. Problems with abstract thinking.

7. Misplacing things.

8. Changes in mood or behavior.

9. Changes in personality.

10. Loss of initiative.

Sometimes people get more agitated. They accuse people with whom they are familiar—their spouses, for example—of stealing things. Sorts of paranoid behavior that sometimes occurs later in the course of the disease. Blaming other people for things that have not occurred in the past. And again I will be talking about this as we go on. The important thing is to evaluate a change in behavior. Obviously people start out at very different levels, so some people can, for example, work on their checkbook and make sure everything is okay, and have done this for years. If they start having a problem with their checkbook, then that is something you have to be concerned about. Other people were never able to balance their checkbook, so you do not have to worry about that. The important thing is really change, what happens over time.

Now why is this a problem? It is a problem because the one thing that we are absolutely sure about is that the major risk factor for Alzheimer's disease is age. This is prevalence, the number of people at any particular time or the percent in this case who have Alzheimer's disease according to age. And it is very clear—all the studies are very consistent—that as you get older your chances of developing Alzheimer's disease increases.

Now why is this important? It is important because the population and the demographics of the United States and, indeed, of the world is changing. Right now about 35 percent of the population is 65 and older. In the next 50 years that is going to more than double. The fastest growing group is actually the over-85 group, and if you look at the demographics here, it is really incredible. About 4.3 million people are 85 and over now. In the next 50 years this will almost quintuple. So if you know that the major risk factor for Alzheimer's disease is age, and the population is aging, then this is a major problem.

Now another aspect is that many of the groups that have been considered minority groups are actually changing in terms of their demographics. If you look at the Hispanic population, for example, the percent of Hispanics in the population over the next 50 years is going to increase. African Americans increases somewhat. Asian and Pacific Islanders. And actually the White non-Hispanic is projected to decrease slightly.

The important aspect of this is that we really do not know a lot about Alzheimer's disease in non-Caucasian populations in terms of whether there are differences or not. There may not be any differences, but some studies are just starting to look at the clinical aspects, the socioeconomic aspects (such as education) and even the potential biological aspects of differences among these various groups in the population.

In fact, the whole world is changing. These are the demographics by age for the world. If you look at the structure of the population, there were very few people 80 and above in 1950. Most were in this lower age range here. In 1995 it has broadened out. By 2050, there are going to be incredible changes in this population group.

Look at the cost of treating disease, right now—well, this was actually in 1992, almost ten years ago. If you look at dementia, which is this bar, the yearly cost for treating dementia is somewhere between $80 and $100 billion. That was ten years ago. So if you look at the changes in the population, and you know that the major risk factor is age, and you all know what it costs for health care. If we do not or if we are not able to treat and eventually prevent Alzheimer's disease, the costs are just going to be incredible.

If we could delay the onset of Alzheimer's disease by five years, we could, in fact, halve the costs. So instead of $100 billion, it would cost $50 billion. Still a lot of money but less than what it *could* cost. So that is why we are trying to find ways, first of all, to understand the disease, because only by understanding the disease will we be able to develop new treatments. Also, over the past five years there has been a lot of discussion and interest in preventing the disease and, in fact, I will tell you at the end about some prevention trials that are actually starting up. One or two have started, a couple more will be starting.

So again what we are thinking about, if you look at this, is that diseases commonly occurring in the elderly play a substantial role in the cognitive functional decline often attributed *solely* to aging. So again what we are going by is the idea that in the absence of disease, cognitive performance is relatively stable in unimpaired elderly, and that cognitive decline, the kinds of things that we see in Alzheimer's disease, is actually a marker for disease.

Alzheimer's disease is not normal aging. It is separate from normal aging. It is a disease which we believe is ultimately treatable and preventable.

So we'll talk about dementia, which is a syndrome of deficits that I mentioned before, we'll talk about normal aging, and I will talk about something which has been called a number of names. We usually call it mild cognitive impairment, or we call it age-associated memory impairment, or benign senescence.

A stage that seems to be intermediate between normal aging and dementia, has recently been a major focus of research and a potential treatment, because of this idea that

if we can diagnose the disease and start treating it before you get major cognitive problems, then this will be a major cost saving and obviously a saving to the individual and to the family.

So there are a number of ways to potentially diagnose Alzheimer's disease. The gold standard, as it were, is postmortem evaluation of the brain after somebody dies. I will be showing you the plaques and tangles which are the hallmarks of the disease. However, a lot of work has been focused on antemortem diagnosis—that is, trying to diagnose the disease before people get the major symptoms and even as early as possible—because once we do have ways to prevent the disease, we will want to give these as early as possible to stop the changes in the brain that ultimately lead to the problems in cognition and behavior.

There are a variety of neuropsychological tests, ways of measuring language, cognition, learning and memory that people have used. I will talk a little bit about neuroimaging, magnetic resonance imaging, and PET imaging, because we believe that these have shown a lot of promise in combination with neuropsychological tests for being able to make a diagnosis before the major cognitive symptoms occur.

There is research going on in trying to evaluate biological markers. That means there are things in the blood or the cerebral spinal fluid that can be used as early diagnostic markers. Right now I think the answer is no, but there is a lot of research going on to try to find that out.

I will also be talking in a little more detail about some genetic markers, because right now we know that there are genes for what is called early onset Alzheimer's disease (that is, before the age of 65) and also at least one gene and probably more that are risk factors for late onset disease.

So early diagnosis, in addition to being able eventually to treat and hopefully prevent the disease, is important for the patient to be able to accept the disease, to learn to manage, to make future living arrangements, and to handle legal and financial arrangements.

I was at a meeting last weekend in Boston in which a videotape was shown of a group consisting of people with mild Alzheimer's disease, in the early stages of the disease. It was really amazing to me to see how well these people understood the disease, were able to articulate what was going on, understood what was going to happen. So even

people who have been diagnosed with the disease can still make reasonable judgments, at least in the beginning, to determine what they want to happen to them, and I think that is very important to take into account.

So let's look at some of the biological aspects of the disease. If we just look at the brain itself, here is a normal brain, and here is a brain from someone who had Alzheimer's disease. As you can see, in the brain from the Alzheimer's patient, these areas between the gray matter, called sulci, are increased. The brain, in general, shrinks because it is losing nerve cells.

You have probably heard of plaques and tangles. Well, this is a nerve cell. Tangles are an abnormal protein which forms inside the nerve cell—and I will show you a little more later—which eventually produces the death of the nerve cell. Plaques are pieces of nerve cells that have degenerated. This would have been the nerve cell, so this is around the nerve cell. There is also a particular protein called β-amyloid, which we think now is very important in terms of producing Alzheimer's disease. And, again, I will talk to you about the β-amyloid. So this is what was outside the nerve cell. This is inside the nerve cell.

And this is a brain. This is the back of the brain. This is the cerebellum. This is the front of the brain. An area that I will be talking about, which is very important to memory, is called the hippocampus. This part of the brain is called the temporal lobe, and the hippocampus seems to be affected very early in the disease. And, in fact, by using neuroimaging techniques, which assess how much the hippocampus is reduced, we may be able to get an early predictor of the disease.

This is a PET scan, or positron emission tomography. It measures the energy use in the brain, the use of glucose, or sugar, in the brain. And this is the PET scan of a normal brain. Red indicates a lot of activity, so normally we see a lot of activity. In moderate Alzheimer's disease the activity reduces. And in severe Alzheimer's disease, activity is reduced even further. So the brain is not using energy. There are areas that are not doing what they are supposed to be doing.

So there are a number of abnormalities in an Alzheimer's disease brain: the deposition of the amyloid precursor protein, which produces the plaques that I told you about; accumulation of parahelical filaments, which produces the tangles.

The problem is that in order for the brain to function, cells have to communicate

with each other. If the cells are dysfunctional, or if they die, they cannot communicate. This is really what produces the symptoms that you see, the decreases in learning and memory, the other problems, behavioral problems. Cells are not talking to each other. The communication is decreased because cells die. There are also other things that happen, and actually these things have provided targets for drug development. We now know that there are inflammatory processes that are going on in the brain. We do not know if these happen early in the course of disease or later in the course of diseases, but there is inflammation. There is also oxidative damage from free radicals. All of these things will produce targets for discovery and development of new drugs.

Now I wanted to put this up. I am not going to test you on this afterwards, but I think it shows the complexity of the disease; there are a lot of things going on. There is death of nerve cells. There is loss of these connections. There are plaques and tangles, deposition of amyloid, decreased blood flow, loss of neurotransmitters, decreased energy metabolism.

What we are trying to figure out is what initiates the disease and what keeps it going, again because if we knew, for example, what initiated the disease in the first place, we would be able to start targeting those processes for new drug development.

What we do know is that the disease starts in the brain many years before the clinical symptoms are evident. We do not know how long, but it may be up to 10 to 20 years or so. These processes are initiated somehow—we do not understand how—in the brain. They go on. At some point they reach a threshold so now you see the symptoms, now you see the memory problems and the other kinds of behavioral problems.

And so again the idea is to try to be able to diagnose as early as possible so that we will be able to produce drugs that will delay the onset or prevent the disease entirely. Obviously, we also want to treat the symptoms and delay the progression. But from this you can see the puzzle that we have.

Let's go back a minute. This protein, β-amyloid, and plaques come from what is called the amyloid precursor protein, which I will show you in a minute. This is a large protein that is cut in a variety of ways to produce b-amyloid. This other protein, the TAO protein, is modified and produces tangles.

These are important to know, because again, once we know how these plaques form from this β-amyloid precursor, we can develop potential ways to reduce them. Now

without getting into a lot of complexity, I just wanted to point out this is a cell. This is the wall of the cell. And this amyloid precursor protein is inserted into the cell. It looks like what you might see when magicians take a balloon and take a pin and put it into the balloon without bursting the balloon. The pin is kind of stuck in the balloon. That is how this amyloid precursor protein is stuck in the cell wall.

Depending upon how the protein is cut, it may produce the plaques and it may not. If it is cut here by one enzyme, no plaques are formed. If it is cut here by two other enzymes, it produces plaques. So now investigators, scientists, know what these enzymes are, and over the past year there have been a number of reports about their identification. Now investigators and pharmaceutical companies are trying to develop drugs that interact with these enzymes and inhibit formation of these plaques. This is an example of how, by understanding the basic biology of the disease, new drugs can be developed which, hopefully, will be able to slow or stop it.

In the same way, TAO—this other protein that leads to tangles—this is a nerve cell process. Here is the nerve cell. The nerve cell makes nutrients that are transported down the cell and these microtubules,—a good way of thinking about these is train tracks—these train tracks transport things up and down the cell. What TAO does is disrupt this so that nutrients cannot get down the cell, and the cell eventually dies. Again, if we can understand this process, how we go from a normal protein to an abnormal protein, hopefully we will be able to develop new drugs which will stop this interference.

A number of studies are focused on trying to understand what factors increase or decrease the risk of disease. As I told you before, aging is the major risk factor. We absolutely know that as you get older, your chances of getting the disease increases. Head injury may or may not be a factor. This is equivocal. As I mentioned before, there may be differences in racial or ethnic groups, and I will show you one example of that. There are a number of genes that have now been associated with the disease. I will also talk a little more later about some protective factors that may be working.

Let me mention the genetics because I think this is important. I think it is instructive to remember that Dr. Alzheimer's paper on the first patient with this disease, which was named after him, came out in 1907. Up until the early 1980s there was essentially no research done on Alzheimer's disease. I mean, it is incredible to think about it. Almost nothing. Starting in the early and mid '80s really is the modern period of Alzheimer's disease. It is only in the past 15 years that we have understood what we now know about the disease and it is only since the early '90s that we understand something

about the genetics of Alzheimer's disease.

Think about two kinds of Alzheimer's disease: early onset, as I mentioned before, which is defined as before the age of 65; and late onset, after the age of 65. There are three genes that are involved in early onset Alzheimer's disease. One on chromosome 21, which is associated with this amyloid precursor protein that I mentioned before, produces the β-amyloid in plaques. There are two other genes, on two other chromosomes, called prescinillens.

Early onset Alzheimer's disease only is about probably five percent of all Alzheimer's disease and in this case it is autosomal dominant, which means if you have the gene you get the disease, but it is very rare, maybe one in 200 families in the United States. That is all.

The important thing about this, however, is that it really gives us information about the late onset because what we know from this is that all these genes are associated with the increase in production of β-amyloid and the increase in plaque formation so that is a very important thing to know.

With respect to late onset disease, we know of one gene—there probably will be other ones. This gene encodes APO LIPO protein E-4. This gene is normally involved in moving cholesterol around the body. What we know that this is a genetic risk factor. This is different from these genes and this is a very important thing to understand. If you have this APO/E-4 gene, your risk of disease is increased but it does not mean that you are going to get the disease. There are people who have the gene that do not get the disease and there are also lots of people who have the disease and do not have the gene. So just because you have this gene does not mean, like these others genes do, that you are going to get the disease, which is why it is not recommended that everyone go out and be tested for this gene, because we really do not know, on an individual basis, what it means. It is helpful to physicians in terms of making a diagnosis if somebody has other symptoms. This may confirm the diagnosis, but by itself it is not diagnostic.

Let me just mention that there are three forms of APO/E—2, 3 and 4—and you get one copy from each of your parents. So you can be 4/4, which is the homozygous, or 3/4. The normal is 3/3. And all this shows is that if you have this 4/4, the age of onset in general is earlier than if you have 3/3. So what it seems to mean is that if you have this APO/E-4 gene, you seem to get the disease earlier. It does not seem to affect the course as far as we know so far.

I wanted to mention this because as I said before, we are just starting to understand potential differences among ethnic and racial groups in terms of Alzheimer's disease and one of the things so far that seems to have held up is that this E-4 gene acts differently in different racial and cultural groups. In the Caucasian population, if you have E-4, your risk goes up.

However, in this one study—and I should point out is just one study—done in Manhattan, the Hispanic population was from the Dominican Republic. In this case, the E-4 gene did not seem to have as much of an effect. However, overall, the prevalence of the disease was greater in the Hispanic and the African American population than the Caucasian population if you just look at this bar.

So, as I said before, it is going to be very important to try to understand if there are differences, in fact, among racial, cultural, and ethnic groups in the risk of the disease and also in the expression of the disease. I think it is fair to say at this point we have some clues but we just do not know for sure.

So in terms of the genes, what we try to understand is, what is normal function of the protein that the gene makes? How do these mutations affect the function? How does this lead to the neuropathology? I mean, these are key questions. How do these genetic changes lead to the pathology and ultimately to the clinical expression of the disease?

A major issue that we really do not understand is the basis for regional vulnerability. Only certain parts of the brain are affected in Alzheimer's disease. The hippocampus, I mentioned before, is one of the first things to be affected. Other areas of the brain, such as the cerebellum, which is involved in body balance and other sorts of things, does not seem to be affected at all. This is a major problem because we really do not understand why this is the case, what it is about certain parts of the brain that make them more vulnerable to the disease process. It is just a total puzzler at this time.

As I mentioned before, there may be protective factors in addition to risk factors. And through studies called epidemiological studies, which look at the population or at people in a particular population who get the disease and do not get the disease and try to figure out what is it about those particular people that increase or decrease their risk of disease, there are two things that have come out which are important in terms of looking at clinical trials.

One is that in a number of studies, people who have used nonsteroidal anti-

inflammatory drugs seem to be at decreased risk of getting the disease. I mentioned before that there does seem to be an inflammatory process in the brains of people who have Alzheimer's disease; it may be that these nonsteroidals are blocking, inhibiting, or slowing down that inflammatory process. It is an area of major research at this point. Another thing from these epidemiological studies is that women who have taken estrogen may be at less risk of developing the disease. Both of these findings have translated into clinical trials. One of which actually was negative, and I will tell you about that, but other ones that are ongoing that, hopefully, will be more positive.

As I mentioned before, the disease process starts early in the brain. We do not know how. Now in people who do not have the disease, they can go through normal aging and maybe forget a couple things and not be quite as sharp but normal. There are people who are super agers with no physical problems, no cognitive problems, and live to be 100. And then there is Alzheimer's disease, where if you look at function, the disease process is started here, but functionally they are fine. At some point they are diagnosed clinically with the disease. There are these symptoms that occur. And over time, eight, ten, or fifteen years, it is variable, there is a total loss of independent function.

As I mentioned before, there seems to be this intermediate stage that we call mild cognitive impairment, which is between normal and dementia. There have been a number of studies over the past five years or so, which have focused in on this stage because again, what we are trying to do is look earlier and earlier in the course of the disease to try to figure out what is going on in the brain so that we can understand these processes and develop treatments.

So let me tell you about a study, which was reported last year, that took a look at mild cognitive impairment and how this changes the risk of Alzheimer's disease. This was a community study done in Rochester, Minnesota, by a researcher at the Mayo Clinic. It looked at 76 people with mild cognitive impairment and evaluated them over a five-year period. What they found was that if researchers looked at general cognition, and they used something called the mini-mental state (although these are general cognitive abilities), that the people with the mild cognitive impairment were reduced somewhat from normal; these are age-matched so these are same age, but Alzheimer's disease was much lower.

However, if researchers looked specifically at memory using a paragraph recall test, where the subjects either read or were read a paragraph, and after certain time passed, they were asked to recall it. In this case the people with mild cognitive impairment looked more like the Alzheimer's patients. Their memory was quite poor. And

what happened as the researchers followed these people over time is that of the people that started out with mild cognitive impairment, about 15 percent per year developed Alzheimer's disease.

In this same population, the same age population, normally about one to two percent of people per year develop the disease. This study was reporting a much higher rate of Alzheimer's disease in these people with mild cognitive impairment. So the criteria which are generally used now for mild cognitive impairment is that there is a memory complaint. There is, in fact, a memory impairment if you test these people. However, they have normal general cognitive function. Normal daily function. They do not have Alzheimer's disease.

So a typical individual might be somebody who is 68 years old, active in the community, drives, handles his or her own finances, but is forgetful, but forgetful beyond normal. That is a very important point. In terms of people who are matched for age, these are people who are below their age match in what you would expect from them for their age.

The conclusion from this study was that mild cognitive impairment can be diagnosed. It is important to identify because these people are at increased risk and they are suitable for treatment studies that might delay the conversion from mild cognative impairment to Alzheimer's disease.

Another way of evaluating mild cognitive impairment is with a test called the Clinical Dementia Rating Test (CDR). I do not want to get into a lot of details, but this is a semi-structured interview in which the interviewer talks to both the patient and the caregiver or the spouse, and the person is evaluated in a number of categories. An overall rating of one is mild Alzheimer's; two is moderate to severe.

But what we want to focus in on is this 0.5. This is questionable Alzheimer's disease or mild cognitive impairment. I wanted to tell you about this because a few of the studies will be saying the 0.5 and I wanted you to understand that that is about the same as the mild cognitive impairment that we have been talking about.

So, first of all, what do the brains of these people look like? Do they look like those with Alzheimer's disease? And, in fact, unfortunately, it does. These are plaques in the brain so if you look at the zero, which is normal, by the time these people have mild cognitive impairment, they have more plaques than normal.

I do want to point out another puzzle. This is a slice of the brain and these are four different individuals who died. Their brains were looked at postmortem. This is the area of the hippocampus that I talked about before. This is the top of the brain. These are people who, based upon their clinical evaluation, were normal. Yet if you look at the numbers of plaques, this person had almost no plaques. This person had some plaques. This person had a lot of plaques. So another puzzle that we are up against is that there is a lot of variability. How is it that somebody who is clinically normal can have all these plaques in the brain? We do not know. In general, it is not the case but there are these peculiar cases.

But with a CDR of 0.5, again questionable, from this study done at Washington University in St. Louis, you can see that already the brain is loaded with plaques and that it has a lot of tangles. So even though the person is at this intermediate stage, their brain still looks like they have Alzheimer's disease.

Another way of evaluating mild cognitive impairment, and again trying to figure out how early in the course of the disease we can diagnose a problem, is by looking at, in this case, magnetic resonance imaging. This is an imaging technique that images the structure of the brain. These brains are actually upside down. This is the top and this is the bottom. This is the area of the hippocampus that I talked to you about before. This is the area that is involved with learning and memory.

So MRI can image the volume of the hippocampus, or how big it is.

So this is a 25-year-old. There is some normal decrease in size of hippocampus. This is actually the brain of Hugh Downs. He agreed to have his brain imaged and he agreed to have people talk about it. This was done at New York University.

Here is the hippocampus of somebody with mild cognitive impairment. Again it is reduced. It is intermediate between normal and Alzheimer's disease. And we think that by imaging the hippocampus and other parts of the brain in this temporal lobe, we may be able to get a way of diagnosing relatively early in the disease.

This was a study done at Mayo Clinic in which they imaged the hippocampuses in people with mild cognitive impairment, and they followed people over time. And what they found out was that people whose hippocampus was of a relatively normal size did not convert to Alzheimer's disease very readily. If your hippocampus was small, again for your age, then your chances of converting to Alzheimer's disease was high. And if the

volume of your hippocampus was intermediate, your chances were intermediate.

These right now are just research tools, but we think that some of these imaging techniques, like magnetic resonance imaging, in conjunction with neuropsychological evaluations will be able to help us diagnose early in the course of the disease.

So now I would like to switch over to some clinical trials to give you some idea of what is going on in terms of trying to both treat the disease in people who have it already but also to either prevent the onset of the disease or prevent the disease entirely.

I am at the National Institute on Aging. There are some other institutes, such as the National Institute of Mental Health, the National Institute of Nursing Research, and the National Institute of Neurological Disorders and Stroke. About a year ago started what is now known as the Alzheimer's Disease Prevention Initiative. What we are trying to do is look at treatment of people with the disease, or secondary prevention, which is treatment of people who already have some aspects of the disease, or mild symptoms, to prevent them from getting worse. We also want to eventually take a look at primary prevention, taking people who are normal or who have a family history, for example, and preventing the disease from occurring.

I showed you, at the beginning, what would happen if we delayed the onset in terms of the cost. If we take the 1997 figures as 100 percent, then again in the next 50 years, the number of people with the disease would more than triple if nothing is done. If you delay the onset by five years in terms of prevalence, that is numbers of people who have the disease, you not only get a cost savings that I showed you before, but again a reduction in the number of people who have the disease.

So there are a number of possible targets for slowing the decline or preventing the disease: looking at antioxidant compounds, anti-inflammatory compounds, estrogens, compounds that help the cells survive, compounds that affect β-amyloid formation or aggregation, and compounds that affect the formation of tangles.

There are three drugs that are on the market right now: Tacrine, which has been around for a while, but is not prescribed very much because of the side effects; another compound called Exelon (phonetic), or Rivastigmine (phonetic), which has just been approved; and another compound called Aricept, or Donepezil, which was approved about two years ago. All of them affect the cholinergic system in the brain. Acetylcholine is a chemical that affects nerve function.

(End Tape, Side A.)

DR. BUCKHOLTZ:—the nerve cells that have this neurotransmitter die and so there is less acetylcholine around. These compounds that are being used to treat the disease are called acetylcholine esterase inhibitors. Basically what they do is boost the amount of acetylcholine in the brain. Results from a study of Donepezil over a one year period showed that it was effective in maintaining function. This is the placebo, this is the Donepezil.

In general, all of these anti-choline esterases are somewhat effective, and maybe more effective in some people than in others, but they do not affect, as far as we know, the disease itself. They affect the symptoms, and that is very important, but what we are also looking for are things that affect the progression of the disease.

I want to quickly tell you about one study that the National Institute on Aging supported looking at vitamin E and another compound in people who were at the CDR 2 stage, or the moderate stage of the disease. It was a two-year study looking at functional outcomes. Instead of simply looking at memory, this study looked at death, institutionalization, loss of activities of daily living or more severe dementia. Basically, what they found was that people who had taken vitamin E delayed worsening of a number of those symptoms by about six months over placebo. This was the first study to show that it was possible to delay the progression of the disease and, in fact, a lot of physicians now are prescribing vitamin E. I would not say go out and start taking it, because this study has not been replicated yet, but it showed that it is possible to delay progression. I think that is important for looking at other compounds as well.

I wanted to talk about Estrogen because there is a lot of interest in estrogen. As I showed you before, there is some indication from the epidemiological studies that women who have taken estrogen are at less risk of developing Alzheimer's disease. We funded a study to see if estrogen would be effective in women who have the disease already; this was a treatment study. This study was a one-year study looking at two doses of Premarin, which is the most widely used estrogenic compound. The outcome would be a clinical measure, or a clinical global improvement of change. That is, did the person improve globally overall from the way they started? There were a number of other outcomes, but this basically was a negative study. This was very disappointing to everybody but, in fact, there was no difference among the low dose, the high dose and the placebo.

What does this mean? Well, these were women who had had hysterectomies. They

were given estrogen. They had the disease. Estrogen did not seem to affect them. It is important to try to understand what this means. There may be different stages of the disease. There may be an initiation stage that begins fairly early, then a stage of progression and by then it may be too late. With people who have the disease already, estrogen does not work. But it does not mean that it may not be possible to prevent the disease in women who do not yet have it, so there are two studies looking at prevention right now.

So although this is disappointing, it points out the importance, I think, of doing clinical trials because it is only through these clinical trials that we really understand whether something really has an effect. The epidemiological studies give us clues but there are a lot of other factors involved in them that are equivocal. It is only by actually doing these clinical studies that we will really know.

Another study, which has just stopped recruiting, was in mild cognitive impairment. This study looked at three treatments—vitamin E, Donepezil, and placebo—to see if any of these would prevent the development of Alzheimer's disease or the decline in cognition over a three-year period. The participants, who have mild cognitive impairment, are now being followed to see if secondary prevention is possible. We know that the mild cognitive impairment in about 15 percent of these people per year will convert to Alzheimer's disease. Do either of these drugs prevent or slow this conversion?

There is a prevention study that is just starting to look at whether a nonsteroidal anti-inflammatory drug, Naproxen—what is called a Cox-2 inhibitor—or one of these newer kinds of anti-inflammatory drugs, Celecoxib, can prevent the disease in people who have a family history of Alzheimer's disease. There are four sites: Hopkins, Boston [not Utah like it says], Arizona, and Rochester, New York. This trial will be the first prevention trial for an anti-inflammatory drug.

There are two prevention trials currently going on to look at estrogen. This one, which takes place at various sites—Columbia, Hopkins, Mayo, and Jacksonville—looks at women who have had hysterectomies and receive estrogen and women who have not had hysterectomies, but get estrogen plus progesterone. These women have a family history of dementia but are not demented. So this is one prevention study. Another is a large NIH prevention study called the Women's Health Initiative and a subset of that called the Women's Health Initiative Memory Study. This study is also looking at whether hormone replacement therapy can prevent the development of Alzheimer's disease.

One last thing I wanted to talk about is a very exciting development that has occurred only over the past year, which is a totally new way of looking at both treatment and prevention of disease, and that is a vaccine study that you may have read about. This was done initially in mice called transgenic mice. These are mice that have the human gene for the amyloid precursor protein, and these mice make plaques. Some of these mice have a memory loss. There is inflammation. Nobody thought that this would work. This is one of these studies which came out of nowhere. Somebody had an idea, tried it, and amazingly, it worked. To see if you could vaccinate these mice with the β-amyloid protein. So the idea was that if we give these mice the β-amyloid protein, they will make antibodies against it, and this will dissolve the plaques.

Well, as I said, nobody thought it would work but, in fact, it did. This is immunization with β-amyloid in these mice. And this is the amount of the amyloid. These are the controls. These are the mice that got the vaccine and their amyloid was reduced significantly. Look at their brains; these are the plaques in the animals that did not get vaccinated. The animals that got vaccinated do not have any plaques.

This really has revolutionized our thinking about treatment and prevention because what happened is that if they gave the vaccine early, the plaques did not develop, but the incredible thing was that if they gave the vaccine to animals who have the plaques already, the plaques went away. So studies have just started in humans. Between this and something that actually works in humans is a long time, but the studies have actually started.

They have tested this in monkeys and there were no safety problems. They have actually done initial safety studies in humans, and again, there do not seem to be any problems so far, so this is going on.

If this really works, if it can be translated from mice to humans, I think it is going to make an incredible change in the way we look at both treatment and prevention of the disease. So it is very exciting.

And there are also these other compounds that I mentioned before, compounds that cut the amyloid precursor protein; those are also in safety trials right now. So there is a lot of work going on.

I want to end by saying again that by understanding the biology of what is going on in the brains of people with Alzheimer's disease and in these other animal models, we

will be able to identify targets for the development of future therapies, so we can prevent the build up of plaques, prevent the build up of tangles, prevent brain cell dysfunction and death.

Other hot areas are early diagnosis, the vaccine, other genetic risk factors, these transgenic models.

So I want to end by this quote from Mark Twain: "When I was younger, I could not remember anything, whether it happened or not, but my faculties are decaying now and soon I should be so I cannot remember any but the things that never happened. It is sad to go to pieces like this but we all have to do it."

Well, maybe we do not all have to do it. Maybe we can, in fact, develop ways so we do not have cognitive decline, so we do not have Alzheimer's disease. I am very optimistic.

Only over the past 15 or 20 years have we come an incredible way in understanding the disease and starting to develop therapies that have treated and actually started looking at ways to prevent it; I am very optimistic that in the fairly near future we will have new ways.

There are a number of places to get more information on aging and Alzheimer's disease, especially the NIA homepage. The National Institute on Aging supports an Alzheimer's Disease Education Referral Center and there is material over here that you can pick up from the ADER center to order things.

There are two clinical trials databases. There is an Alzheimer's disease clinical trial database, http://www.alzheimers.org, and an NIH clinical trials database, http://clinicaltrials.gov. I did not have the Alzheimer's Association's database. It is http://www.alz.org. So there are a number of sources of information available on Alzheimer's disease that I think can be very useful. So thank you very much.

(Applause.)

DR. BUCKHOLTZ: Questions? I think they wanted us to use the microphone but what I will do is I will just repeat the question.

(Inaudible--Someone not at a microphone asks a question).

DR. BUCKHOLTZ: The question is how much should you be taking? I cannot make recommendations because we really, unfortunately, do not know at this point. I think once these clinical trials are done we will have a better idea. I would obviously not recommend taking them—the NSAIDS have other problems. They can have major serious side effects.

(Inaudible--Someone not at a microphone asks a question).

DR. BUCKHOLTZ: Even the Celebrex. There are two cox-2 inhibitors: Celebrex and Vioxx.

(Inaudible).

(Inaudible--Someone not at a microphone asks a question).

DR. BUCKHOLTZ: And the other nonsteroidals. I think only under a physician's guidance should you be taking those.

As far as vitamin E, generally, people are taking now maybe 400 international units a day. It is probably a reasonable amount. But again you have to be careful in terms of other things because vitamin E is a blood thinner. It affects platelets, so if you are taking aspirin or especially other blood thinners you have to be very careful. So even though it is over the counter, it is something that you should probably talk about to your physician about.

(Inaudible--Someone not at a microphone asks a question).

DR. BUCKHOLTZ: The question was, is there a basic difference between AIDS and dementia? Yes, absolutely. There is an AIDS dementia, because in AIDS, the brain is affected by the virus, but that is very specific—dementia is a general term.

(Inaudible--Someone not at a microphone asks a question).

DR. BUCKHOLTZ: Dementia is a general term. Alzheimer's disease is a type of dementia. There are other types of dementia like stroke, vascular dementia and other things.

(Inaudible--Someone not at a microphone asks a question).

DR. BUCKHOLTZ: The question is about a combination. That is an excellent question and we do not know. Those studies are difficult to do, and somebody has suggested a combination, actually, but no study has yet been done looking at the combination. It makes a lot of sense to combine these different kinds of things—the antioxidants, the anti-inflammatories, the estrogen in women—but nobody has done that yet.

(Inaudible--Someone not at a microphone asks a question).

DR. BUCKHOLTZ: The question is about raloxifene, which is an estrogenic kind of compound. There have not been any good studies yet to determine the effects of raloxifene on dementia. Some evaluations are being done. There have been large studies of raloxifene for other diseases, and there have been some evaluations of cognition done in those studies but I do not think there is any firm conclusion yet. These are called selective SERMs or selective estrogen receptor modulators. And it is a very important area, but there are no specific studies done yet to find out.

(Inaudible--Someone not at a microphone asks a question).

DR. BUCKHOLTZ: Yes. Absolutely. I should have mentioned that. There are studies looking at social and behavioral aspects of the disease as well. I should mention that in addition to the obvious cognitive problems, there are many other behavioral problems in Alzheimer's disease in other dimensions such as aggression, agitation, sleep disorders, and wandering. There are psychotic problems like hallucinations and delusions. Some of these may be able to be treated by drugs, but the drugs that are currently available are not very good at treating any of these. There are studies being done to look at behavioral interventions and also environmental sorts of interventions, and a variety of other things, which are very important to look at the potential modification of those behaviors as well.

(Inaudible--Someone not at a microphone asks a question).

DR. BUCKHOLTZ: I think it is very important that you consult your physician because vitamin E is a kind of anticoagulant, and if you are taking aspirin or warfarin or other anticoagulants, it can be bad for you. We tend to think that because something is available over the counter or at GNC it is okay to take it, and it may be, but again, it is very important to evaluate, with your physician, what other things you are taking and see if there are potential interactions among those things.

(Inaudible--Someone not at a microphone asks a question).

DR. BUCKHOLTZ: Well, that is a good question. We think Alzheimer's disease has always been there. It's just that not many people were old enough to develop the disease and now, with the large number of older people, we are seeing more and more of it. So it has probably been there all along. It has just not been as evident because there just were not that many older people around to see.

(Inaudible--Someone not at a microphone asks a question).

DR. BUCKHOLTZ: A good question: why do some people develop AD and some people do not? We do not know. It could be because of some of these risk factor genes. It could be because of some environmental aspects. We just really do not know why it is and that is why it is so important to try to do these epidemiological kinds of studies to get at least clues to what may be risk and protective factors, then figure out the genetics.

Geneticists believe that at least four other risk factor genes are going to be discovered over the next five to ten years. And these may interact in some way with other genes. We just do not know. It is too early to say.

(Inaudible--Someone not at a microphone asks a question).

DR. BUCKHOLTZ: Another good question: are there lifestyle differences? One thing that has come out of the epidemiological studies is that people who have a higher education and a higher occupational level seem to be at less risk of developing the disease. Now we do not know why.

We do not know if that is a biological effect. There are more connections made. We do not know if there is some socioeconomic aspect to that. We just do not know. But this is an important issue that people are trying to focus in on. Are there socioeconomic differences? Are there lifestyle differences?

An epidemiological study came out last year indicating that there might have been differences between people who grew up in a rural versus an urban population. These are all questions that we are trying to understand. I think, though, that an important thing is to keep active as you age, to learn new things. It certainly cannot hurt and it probably will help you a lot so that is very important.

(Inaudible--Someone not at a microphone asks a question).

DR. BUCKHOLTZ: In terms of diet, there are probably some good things: antioxidants, blueberries, strawberries. There have been animal studies.

(Laughter.)

DR. BUCKHOLTZ: Seriously. There have been animal studies that have indicated that older animals who eat blueberries and strawberries do better on certain cognitive tests. Now it may be because they are antioxidants. I do not know.

The one thing actually that may be important is fat in your diet. These transgenic animals who are on a high-fat diet get more plaques in their brain, so there may be some connection there. Again it is an important issue. People are looking at it. We do not know yet.

(Inaudible--Someone not at a microphone asks a question).

DR. BUCKHOLTZ: In terms of plaques and tangles, as far as we know right now, no behavioral ways. That is why the focus has been on some of these drugs that may be able to modify them, but not at this point.

(Inaudible--Someone not at a microphone asks a question).

DR. BUCKHOLTZ: As far as alcohol and drug abuse, it is probably not good for you, but I do not know that there is any specific connection.

(Inaudible--Someone not at a microphone asks a question).

DR. BUCKHOLTZ: Alcohol probably kills brain cells. Again, it is not clear exactly how that works, but as we know, too much alcohol is not good for you. Although some epidemiological studies, for what they are worth, indicate that people who drink alcohol moderately have less risk of Alzheimer's disease. The problem with these epidemiological studies is that they give us clues, but you cannot do a clinical trial on alcohol.

(Inaudible--Someone not at a microphone asks a question).

DR. BUCKHOLTZ: One of the studies that I did not mention is a prevention study that is ongoing, now funded through the National Center for Complementary and Alternative Medicine to look at whether gingko can prevent Alzheimer's disease. This is a fairly high dose of gingko, 240 milligrams, I think, over a five year period to see. Some of these supplements, these antioxidants and other sorts of things, may, in fact, be quite useful. Again we just need to do trials on it.

(Inaudible--Someone not at a microphone asks a question).

DR. BUCKHOLTZ: Some very interesting animal studies and at least one human study have shown that some kinds of physical activity are actually very important in brain function. Again, this is an area which is just starting to be looked at. Studies have shown that animals that are more physically active actually develop new brain cells in certain areas of the brain. The one study in humans has shown that aerobic physical activity, but not stretching, helped in certain brain functions. This is certainly an area that needs to be looked at a lot more in terms of those kinds of relationships.

(Inaudible--Someone not at a microphone asks a question).

DR. BUCKHOLTZ: Some people think that gamma tocopherol may be a better antioxidant than alpha. In fact, we are just starting to fund one small study to look at that. What is it about these antioxidants? Are some antioxidants better than others? These are good questions that just need more study.

(Inaudible--Someone not at a microphone asks a question).

DR. BUCKHOLTZ: That is a good question: what do plaques actually mean? Some people think that plaques are simply a tombstone. That by the time you have a plaque you can't do anything. Other people believe that the plaques themselves are toxic. Other people believe that the forms of β-amyloid, before they actually aggregate or early aggregation forms, are the things that are actually toxic and kill nerve cells.

We're not absolutely certain. There is a lot of work that is going on to try to understand what is, in fact, the toxic factor that actually produces the dysfunction and the death of cells.

Again, let me thank you very much. There is material up here if you have not gotten it already.

(Applause.)

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